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The role of MAPK and SCF in the destruction of Med13 in cyclin C mediated cell death.

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In response to stress, the yeast [1] and mammalian [2] cyclin C translocate from the nucleus to the cytoplasm, where it associates with the GTPase Drp1/Dnm1 to drive mitochondrial fragmentation and apoptosis. Therefore, the decision to release cyclin C represents a key life or death decision. In unstressed cells, the cyclin C-Cdk8 kinase regulates transcription by associating with the Mediator of RNA polymerase II. We previously reported that that the Mediator component Med13 anchors cyclin C in the nucleus[3]. Loss of Med13 function leads to constitutive cytoplasmic localization of cyclin C, resulting in fragmented mitochondria, hypersensitivity to stress and mitochondrial dysfunction due to

loss of mtDNA. Recently we showed that this molecular switch operates in a two step process. First, efficient cyclin C nuclear release requires its ROS-induced phosphorylation by the MAP kinase Slt2 [4] in a carboxyl terminal region of cyclin C, which includes a putative Med13 interaction site. The second step involves ROS-induced Med13 destruction by the SCF^{Grr1} ubiquitin ligase. Med13 associates with Grr1 in two-hybrid assays, and SCF mediated degradation of Med13 requires active cyclin C-Cdk8[5]. However, phosphorylation of Med13 by cyclin C-Cdk8 does not trigger Med13 destruction. This suggests a model in which this kinase primes the Med13 degron for SCF^{Grr1} and either Slt2, or an as yet unidentified kinase, triggers its destruction. Taken together, these results are consistent with a model in which cyclin C phosphorylation by Slt2 permits its disassociation from Med13, and that Med13 destruction allows full cyclin C release and prevents re-accumulation of the cyclin in the nucleus.

[1]Dev. Cell. (2014), 28:161; [2]Mol. Biol. Cell. (2015), 26:1030; [3]Mol. Biol. Cell (2104) 25:2807; [4]Mol. Biol. Cell. (2014) 25:1396; [5]MB0C. (2017) submitted

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